Rhodium-catalyzed oxidative coupling of aromatic imines with internal alkynes *via* regioselective C–H bond cleavage†

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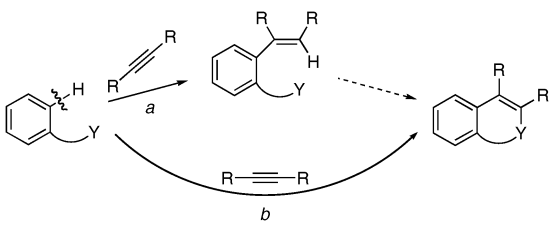
The rhodium-catalyzed oxidative coupling of aromatic imines with alkynes effectively proceeds *via* regioselective C–H bond cleavage to produce indenone imine and isoquinoline derivatives.

Transition metal-catalyzed organic reactions *via* C–H bond cleavage have attracted much attention from an atom-economic point of view, and various catalytic processes involving different modes to activate the ubiquitously available bond have been developed.[1] Among the most promising activation strategies is utilization of the proximate effect by coordination of a functional group in a given substrate to the metal center of a catalyst, which brings about regioselective *ortho* C–H bond activation and functionalization. Particularly, reactions using alkynes as a coupling partner are useful as methods for the synthesis of *ortho*-vinylated aromatic compounds, which are important precursors of various condensed aromatic and heteroaromatic derivatives (Scheme 1, path a). As precedent examples, the *ortho*-vinylation reactions of ketones,[2] naphthols,[3] imines[4] and azobenzenes[5] have been developed.

Meanwhile, oxidative coupling *via* C–H bond cleavage appears to be an advanced method to produce such benzannulated compounds in one step, simply and directly (Scheme 1, path b). We have succeeded in conducting the oxidative coupling of benzoic acids[6] and salicylaldehydes[7] with alkynes efficiently under rhodium catalysis to afford isocoumarin and chromone derivatives, respectively. More recently, Fagnou *et al.* reported the synthesis of indoles from anilides by using a related catalyst system.[8] During our further study of rhodium-catalyzed oxidative coupling,[9] it has been revealed that the oxidative coupling of aromatic imines such as benzylideneanilines and benzophenone imine with alkynes can also be performed to form indenone imine and isoquinoline derivatives, respectively.[10,11] These compounds are useful as synthetic intermediates for various fine chemicals including medicines and organic materials.[12]



Scheme 1 Synthesis of condensed (hetero)aromatic compounds *via* regioselective C–H bond cleavage.

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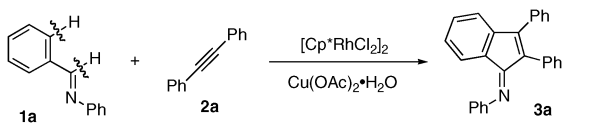
In an initial attempt, benzylideneaniline (**1a**) (0.5 mmol) was treated with diphenylacetylene (**2a**) (0.5 mmol) under conditions similar to those employed for the coupling of benzoic acids with **2a**.[6c,d] Thus, in the presence of $[Cp^*RhCl_2]_2$ (0.005 mmol) and $Cu(OAc)_2 \cdot H_2O$ (1 mmol) in *o*-xylene (3 mL) at 80 °C under N_2, *N*-(2,3-diphenyl-1*H*-inden-1-ylidene)benzenamine (**3a**) was formed in only 4% yield after 10 h (entry 1 in Table 1; Cp* = pentamethylcyclopentadienyl). In DMF, the product yield dramatically increased to 61% (entry 2), and the use of an excess amount of **1a** (1 mmol) improved the product yield slightly (entry 3). A comparable result was obtained at 100 °C, while the yield of **3a** was slightly decreased at 60 °C (entries 4 and 5). Finally, the yield was enhanced up to 85% by increasing the amount of $[Cp^*RhCl_2]_2$ to 1 mol% (entry 6). The present reaction was, however, sluggish under air with a catalytic amount of the copper species (entry 7).

Table 2 summarizes the results for the reactions of various benzylideneanilines **1a–g** with internal alkynes **2a–e**. Chloro-, methyl- and methoxy-substituted benzylideneanilines **1b–f** reacted with **2a** smoothly to produce the corresponding indenone imines **3b–f** in 71–99% yields (entries 1–5). *N*-(2-Naphthylmethylene)-aniline (**1g**) underwent the coupling with **2a** to selectively give **3g** in 97% yield (entry 6). However, an *N*-alkylimine, benzylidene-*tert*-butylamine, was recovered almost quantitatively under similar conditions. The reactions of **1a** with diarylacetylenes **2b–d** or

Table 1 The reaction of *N*-benzylideneaniline (**1a**) with diphenylacetylene (**2a**)[a]



Entry	**1a**/mmol	$[Cp^*RhCl_2]_2$/mmol	Temp/°C	Time/h	Yield of **3a** (%)[b]
1[c]	0.5	0.005	80	10	4
2	0.5	0.005	80	10	61
3	1	0.005	80	10	67
4	1	0.005	60	10	56
5	1	0.005	100	2	65
6	1	0.01	80	6	85 (76)
7[d]	1	0.01	80	6	28

[a] *Reaction conditions:* **2a** (0.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (1 mmol), DMF (3 mL) under N_2. [b] GC yield based on the amount of **2a** used. Value in parentheses indicates yield after purification. [c] In *o*-xylene. [d] Using $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol) under air.

Table 2 The reaction of *N*-(arylmethylene)anilines **1** with alkynes **2**[a]

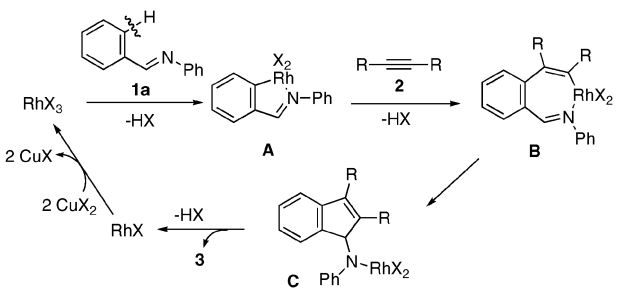
Entry	1	2	Time/h	Product, yield (%)[b]
1	**1b**: R^1 = Cl; R^2 = H	**2a**	10	**3b**: R^1 = Cl; R^2 = H, 82 (78)
2	**1c**: R^1 = Me; R^2 = H		6	**3c**: R^1 = Me; R^2 = H, 83 (83)
3	**1d**: R^1 = H; R^2 = Cl		6	**3d**: R^1 = H; R^2 = Cl, 99 (99)
4	**1e**: R^1 = H; R^2 = OMe		8	**3e**: R^1 = H; R^2 = OMe, 71 (54)
5	**1f**: R^1 = Cl; R^2 = Cl		10	**3f**: R^1 = Cl; R^2 = Cl, 86 (86)
6	**1g**	**2a**	4	**3g**, 97 (91)
7	**1a**	**2b**: X = Cl	4	**3h**: X = Cl, 65 (65)
8		**2c**: X = Me	4	**3i**: X = Me, 68 (65)
9		**2d**: X = OMe	4	**3j**: X = OMe, 46 (45)
10	**1a**	**2e**	12	**3k**, 40 (32)

[a] *Reaction conditions:* **1** (1 mmol), **2** (0.5 mmol), $[(Cp^*RhCl_2)_2]$ (0.01 mmol), $Cu(OAc)_2{\cdot}H_2O$ (1 mmol), DMF (3 mL) at 80 °C under N_2. [b] GC yield based on the amount of **2** used. Value in parentheses indicates yield after isolation.

4-octyne (**2e**) also proceeded to afford **3h–3k**, respectively (entries 7–10). In contrast to such internal alkynes, 1-phenylacetylene did not couple with **1a** at all, and an alkyne dimer, diphenylbutadiyne, was formed quantitatively.

A plausible mechanism for the reaction of benzylideneaniline (**1a**) with alkynes **2** is illustrated in Scheme 2, in which neutral ligands are omitted for clarity. In the first step, coordination of the nitrogen atom of **1a** to an $Rh^{III}X_3$ species appears to be a key step for the regioselective C–H bond cleavage to afford **A**. Then, alkyne insertion to form **B**, intramolecular insertion of the imino moiety to form **C**, and β-hydrogen elimination may successively occur to give product **3**.[13] The $Rh^{I}X$ species, formed by release of HX, may be oxidized by a copper(II) salt to regenerate $Rh^{III}X_3$.

Under similar conditions, benzophenone imine (**4**) was found to very efficiently undergo the oxidative coupling with alkynes **2** (Table 3). Thus, treatment of **4** (0.5 mmol) with **2a** (0.5 mmol) in the presence of $[Cp^*RhCl_2]_2$ (0.005 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (1 mmol) in DMF (3 mL) at 80 °C under N_2 for 2 h gave 1,3,4-triphenylisoquinoline (**5a**) in 98% yield (entry 1). Similarly, 3,4-diaryl- and 3,4-dipropyl-2-phenylisoquinolines **5b–e** were obtained in good yields by the reactions of **4** with **2b–e** (entries 2–5). 1-Phenylpropyne (**2f**) also reacted with **4** to give 4-methyl-1,3-diphenylisoquinoline (**5f**), along with a small amount

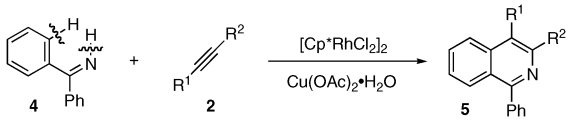


Scheme 2 A plausible mechanism for the reaction of **1a** with **2**.

of an unidentified isomer (**5f** : isomer = 89 : 11) (entry 6). Compound **5f** was separable from the isomer and isolated in 85% yield. In contrast to free-nitrogen imine **4**, benzophenone phenylimine (**6**) did not undergo oxidative coupling with **2a** under similar conditions. In this case, only *ortho*-vinylation (Scheme 1, path a) took place to form a non-oxidative coupling product **7** (Scheme 3).

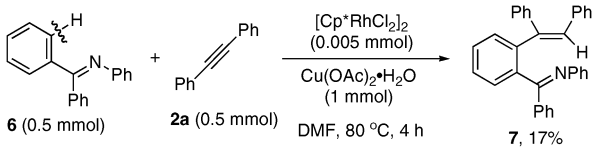
As depicted briefly in Scheme 4, isoquinoline **5** may be formed *via* five-membered (**D**) and seven-membered (**E**) rhodacycle intermediates. Meanwhile, the reaction of *N*-substituted imine **6** seems to proceed *via* intermediates **A′**

Table 3 The reaction of benzophenone imine (**4**) with alkynes **2**[a]

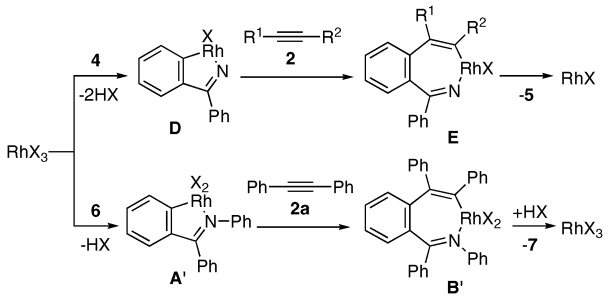


Entry	2	R^1	R^2	Product, yield (%)[b]
1	**2a**	Ph	Ph	**5a**, 98 (90)
2	**2b**	4-ClC_6H_4	4-ClC_6H_4	**5b**, 86 (86)
3	**2c**	4-MeC_6H_4	4-MeC_6H_4	**5c**, 99 (92)
4	**2d**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**5d**, 95 (95)
5	**2e**	Pr	Pr	**5e**, 85 (85)
6	**2f**	Me	Ph	**5f**, 99[c] (85)

[a] *Reaction conditions:* **2** (0.5 mmol), **4** (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol), $Cu(OAc)_2 \cdot H_2O$ (1 mmol), DMF (3 mL) at 80 °C for 2 h under N_2. [b] GC yield based on the amount of **2** used. Value in parentheses indicates yield after purification. [c] Contaminated with an isomer (**5f** : isomer = 89 : 11).



Scheme 3 The reaction of benzophenone phenylimine (**6**) with **2a**.



Scheme 4 A plausible mechanism for the reactions of **4** and **6** with **2**.

and **B′**, related to **A** and **B** in Scheme 2, rather than **D** and **E**. Then, protonolysis of the C–Rh bond in **B′** may occur, in preference to intramolecular insertion of the sterically hindered imino moiety, to afford **7**.

In summary, we have demonstrated that the rhodium-catalyzed oxidative coupling of aromatic imines with alkynes proceeds efficiently accompanied by regioselective C–H bond cleavage. These reactions provide straightforward routes to benzannulated compounds such as indenone imine or isoquinoline derivatives, which are useful intermediates for medicines and organic materials.

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